UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,333	03/25/2004	Alan J. Heeger	327823-1052	8242

38706 7590 04/03/2007

FOLEY & LARDNER LLP
1530 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER	
CROW, ROBERT THOMAS	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,333	HEEGER ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,8,12-16,25 and 28-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,8,12-16,25 and 28-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/04; 1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 29 January 2007 in which claims 1, 7, and 25 were amended, claims 4-6 and 35-38 were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The objections to the specification listed in the previous Office Action are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

In view of Applicant's request on page 17 of the Remarks that the request for a terminal disclaimer be held in abeyance, the previous rejections under the judicially created doctrine of obviousness-type double patenting over claims 1-14 of copending Application No. 11/193,318 are **maintained** for the reasons set forth in the previous Office Action.

The previous rejections under the judicially created doctrine of obviousness-type double patenting over copending Application 10/678,760 are withdrawn in view of Applicant's abandonment of the conflicting application.

Claims 1, 7-8, 12-16, 25, and 28-34 are under prosecution.

Information Disclosure Statement

2. The Information Disclosure Statement filed 25 January 2007 is acknowledged.

3. Applicant notes on page 5 of the Remarks filed 21 November 2006 that the citation of the Abstracts of documents CN1422960 (China) and CN1422961 (China) on the IDS of 18 November 2004. The examiner has initialed the IDS and included it with this Office Action. However, the remaining references are already on the record, and have been lined through to avoid duplication.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 7-8, 14, and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001).

This is a new rejection necessitated by the amendments.

Regarding claim 1, Lee et al teach a detector for determining the presence of an oligonucleotide target having a target nucleotide sequence (Abstract). In a single exemplary embodiment, Lee et al teach an electrode capable of sensing redox events in a redox moiety in the form of electrodes in a microreaction vessel (page 19, line 36-page 20, line 8) and a probe immobilized on the electrode (page 4, line 35-page 14, line 2). The probe carries a redox moiety (page 12, lines 5-9) and has a nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9). Lee et al further teach the probe is a molecular beacon, which forms a hairpin in the absence of a complementary target sequence; after hybridization to the target, a pair of labels are separated (page 3, lines 24-31) and said hybridization results in a change in the redox properties of a pair of labels that are detectable because the results are recorded electrochemically (page 12, lines 5-9). Thus the probe has a first configuration in the absence of hybridization with the target polynucleotide, which locates the redox moiety in a first position relative to the electrode and has a second configuration, in the presence of hybridization with the target polynucleotide, which locates the redox moiety in a second position relative to the electrode.

Regarding claim 7, Lee et al teach the detector of claim 1 wherein the probe is immobilized on the on the electrode at a position distant from the redox moiety; namely, the redox moiety is the label within the pair of labels that is the furthest from the electrode (page 3, lines 24-31).

Regarding claim 8, Lee et al teach the detector of claim 1 wherein the electrode is capable of inducing redox events in the redox moiety; namely, application of an electrochemical potential is applied to induce hybridization (page 17, lines 19-32), wherein the hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically (page 12, lines 5-9).

Regarding claim 14, Lee et al teach the detector of claim 1 wherein the electrode comprises a metal (page 8, lines 15-21).

Regarding claim 16, Lee et al teach the detector of claim 1 wherein the redox moiety is ethidium bromide (page 15, lines 5-15).

Response to Arguments

Applicant's arguments on pages 6-10 of the Remarks with respect to the rejections of the claim as anticipated by, or obvious in view of, Blackburn et al have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly

owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Egholm et al (U.S. Patent No. 6,451,588 B1, issued 17 September 2002).

This is a new rejection necessitated by the amendments.

Regarding claim 12, Lee et al teach the detector of claim 1 for determining the presence of an oligonucleotide target having a target nucleotide sequence (Abstract). In a single exemplary embodiment, Lee et al teach an electrode capable of sensing redox events in a redox moiety in the form of electrodes in a microreaction vessel (page 19, line 36-page 20, line 8) and a probe immobilized on the electrode (page 4, line 35-page 14, line 2). The probe carries a redox moiety (page 12, lines 5-9) and has a nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9). Lee et al further teach the probe is a molecular beacon, which forms a hairpin in the absence of a complementary target sequence; after hybridization to the target, a pair of labels are separated (page 3, lines 24-31) and said hybridization results in a change in the redox properties of a pair of labels that are detectable because the results are recorded electrochemically (page 12, lines 5-9). Thus the probe has a first configuration in the absence of hybridization with the target polynucleotide, which locates the redox moiety in a first position relative to the electrode and has a second configuration, in the presence of hybridization with the target polynucleotide, which locates the redox moiety in a second position relative to the electrode.

Lee et al are silent with respect to internal hybridization in the second conformation.

However, Egholm et al teach immobilized nucleic acid probes (column 15, lines 40-53) wherein upon hybridization to the target, the probe comprises internal hybridization; namely, Figures 4C and 4D, where the probe is a pair of probes (Figure 4C) that, upon hybridization to target 20, has a hybridization region maintained between probes 44 and 46 (column 12, lines 1-13) with the added advantage of allowing use of two low-complexity libraries having less that 0.005% of the probes required by a single high-complexity library (column 14, lines 24-47).

It would therefore have been obvious to a person or ordinary skill in the art at the time the claimed invention was made to have modified the detector as taught by Lee et al with the probes as taught by Egholm et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a detector having the added advantage of allowing use of two low-complexity libraries having less that 0.005% of the probes required by a single high-complexity library as explicitly taught by Egholm et al (column 14, lines 24-47).

9. Claims 1 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Rothberg et al (U.S. Patent Application Publication No. US 2002/0012930 A1, published 31 January 2002).

This is a new rejection necessitated by the amendments.

Regarding claim 12, Lee et al teach the detector of claim 1 for determining the presence of an oligonucleotide target having a target nucleotide sequence (Abstract). In a single exemplary embodiment, Lee et al teach an electrode capable of sensing redox events in a redox moiety in the form of electrodes in a microreaction vessel (page 19, line 36-page 20, line 8) and a probe immobilized on the electrode (page 4, line 35-page 14, line 2). The probe carries a redox moiety (page 12, lines 5-9) and has a nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9). Lee et al further teach the probe is a molecular beacon, which forms a hairpin in the absence of a complementary

target sequence; after hybridization to the target, a pair of labels are separated (page 3, lines 24-31) and said hybridization results in a change in the redox properties of a pair of labels that are detectable because the results are recorded electrochemically (page 12, lines 5-9). Thus the probe has a first configuration in the absence of hybridization with the target polynucleotide, which locates the redox moiety in a first position relative to the electrode and has a second configuration, in the presence of hybridization with the target polynucleotide, which locates the redox moiety in a second position relative to the electrode.

Lee et al do not teach loops in the target and the probe in the second conformation (i.e., during hybridization).

However, Rothberg et al teach probes hybridized to targets wherein the probe and the target have a loop during hybridization; namely, Figure 1D, wherein the hybridized rolling circle probe leaves a loop in the target in the form of the gapped region and a loop in the form of the single stranded portion of the rolling circle template molecule (Figure 1D). Rothberg et al teach the loop in the target has the added advantage of allowing detection of single nucleotide polymorphisms in the gap (paragraph 0091). Rothberg et al further teach the rolling circle probe has the added advantage of allowing isothermal amplification to generate thousands of copies of the target nucleic acid (paragraph 0087).

It would therefore have been obvious to a person or ordinary skill in the art at the time the claimed invention was made to have modified the detector as taught by Lee et al with the probes comprising the loop regions in the target and the probe as taught by Rothberg et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a detector having the added advantage of allowing detection of single nucleotide polymorphisms in the gap, as well as the additional added advantage of allowing isothermal amplification to generate thousands of copies of the target nucleic acid as explicitly taught by Rothberg et al (paragraphs 0091 and 0087).

10. Claims 1 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Hashimoto (U.S. Patent Application Publication No. US 2001/0024788 A1, issued 27 September 2001).

This is a new rejection necessitated by the amendments.

Regarding claim 15, Lee et al teach the detector of claim 1 for determining the presence of an oligonucleotide target having a target nucleotide sequence (Abstract). In a single exemplary embodiment, Lee et al teach an electrode capable of sensing redox events in a redox moiety in the form of electrodes in a microreaction vessel (page 19, line 36-page 20, line 8) and a probe immobilized on the electrode (page 4, line 35-page 14, line 2). The probe carries a redox moiety (page 12, lines 5-9) and has a nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9). Lee et al further teach the probe is a molecular beacon, which forms a hairpin in the absence of a complementary target sequence; after hybridization to the target, a pair of labels are separated (page 3, lines 24-31) and said hybridization results in a change in the redox properties of a pair of labels that are detectable because the results are recorded electrochemically (page 12, lines 5-9). Thus the probe has a first configuration in the absence of hybridization with the target polynucleotide, which locates the redox moiety in a first position relative to the electrode and has a second configuration, in the presence of hybridization with the target polynucleotide, which locates the redox moiety in a second position relative to the electrode.

While Lee et al further teach the detector wherein the electrode comprises a metal (i.e., claim 14; page 8, lines 15-21), Lee et al are silent with respect to gold.

However, Hashimoto teaches a nucleic acid carrier for electric detection of nucleic acids (Abstract) comprising gold electrodes and immobilized thiolated nucleic acids with the added advantage that gold is preferable for immobilizing sulfur-bearing nucleic acids because of the high affinity of gold for sulfur (paragraph 0032).

It would therefore have been obvious to a person or ordinary skill in the art at the time the claimed invention was made to have modified the detector comprising metal electrodes as taught by Lee et al with the gold electrodes as taught by Hashimoto with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a detector having the added advantage of having high affinity immobilization of nucleic acids to the electrodes as explicitly taught by Hashimoto (paragraph 0032).

10. Claims 25, 28-32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Lizardi et al (U.S. Patent No. 5,312,728, issued 17 May 1994).

This is a new rejection necessitated by the amendments.

Regarding claims 25, 28-32, and 34, Lee et al teach a detector for determining the presence of a target polynucleotide having a target nucleotide sequence (Abstract). In a single exemplary embodiment, Lee et al teach an electrode capable of sensing redox events in a redox moiety in the form of electrodes in a microreaction vessel (page 19, line 36-page 20, line 8) and polynucleotide probe immobilized on the electrode (page 4, line 35-page 14, line 2). The probe carries a redox moiety (page 12, lines 5-9) and has a nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9).

Lee et al also teach the detector additionally comprises a detector and an indicator for inducing redox events in the redox moiety; namely, the indicator is a potentiostat (page 19, lines 12-35) for application of an electrochemical potential that induces hybridization (page 17, lines 19-32), wherein the hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically (i.e., claim 29; page 12, lines 5-9). The recording is done by a measurement means, which is the detector for detecting electron transduction (i.e., claim 28; page 7, lines 20-35).

Lee et al further teach the detector wherein the electrode comprises a metal (i.e., claim 32; page 8, lines 15-21) and the redox moiety is ethidium bromide (i.e., claim 34' page 15, lines 5-15).

Lee et al also teach the probes are molecular beacons (page 3, lines 24-31), which form hairpins in the in the absence of a complementary target sequence; after hybridization to the target, a pair of labels are separated (page 3, lines 24-31) and said hybridization results in a change in the redox properties of a pair of labels that are detectable because the results are recorded electrochemically (page 12, lines 5-9). Thus, the probe has a first configuration in the absence of hybridization with the target polynucleotide, which locates the redox moiety in a first position relative to the electrode and has a second configuration, in the presence of hybridization with the target polynucleotide, which locates the redox moiety in a second position relative to the electrode.

Lee et al also teach the detector wherein the probe is immobilized on the on the electrode at a position distant from the redox moiety; namely, the redox moiety is the label within the pair of labels that is the furthest from the electrode (page 3, lines 24-31). Thus, the probe of Lee et al has a first region in the form of the end that is immobilized to the electrode (i.e., claim 30), and a third region that is the second end of the probe, where the redox moiety is attached.

While Lee et al teach the internal structure of the intervening second region has a loop wherein the target binds (page 3, lines 24-31), Lee et al do not teach any further internal structure of the second region.

However, Lizardi et al teach a probe nucleic acid that is a single molecule (e.g., column 14, Example V and Figures 12-13). Figure 12 illustrates the probe 30 in the absence of an oligonucleotide target, and Figure 13 shows the alternate conformation of the probe in the presence of the target (column 14, Example V). Lizardi et al teach the probe has switch sequences, which hybridize to each other in the absence of a target (column 5, lines 45-50). Figure 12 comprises element 32, which comprises the first region. Lizardi et al also teach switch sequences and probe sequences overlap (column 7, lines 47-55); thus, the second region of the instantly claimed probe comprises the remainder of element 32 as well as elements 33 and 34. The second region self hybridizes to form first loop 31 and a stem between part of 32

and 33, which are the first and second nucleotide sequences. The third region of the probe is element 35, which is located at the other end of the probe.

Figure 13 shows that upon hybridization to oligonucleotide target 8, loop 31, which is the probe sequence, is hybridized to the target. Because Lizardi et al teach switch sequences and probe sequences overlap (column 7, lines 47-55), part of 32, which is the first nucleotide sequence, also hybridizes to the target. The remaining part of 32, which is in the second region, hybridizes to part of 34, which is also part of the second region, thereby forming second loop 33 in the detectable ribozyme structure of Figure 13 (column 14, Example V). Lizardi et al also teaches the probes have the added advantage of allowing exponential replication of the target polynucleotide (column 14, lines 40-41), which generates up to a billion copies of a single target molecule in a single step (column 3, lines 48-50). Thus, the threshold of sensitivity of the detector is extended to the level of a single molecule.

It would therefore have been obvious to a person or ordinary skill in the art at the time the claimed invention was made to have modified the detector comprising probes as taught by Lee et al with the loop forming probe as taught by Lizardi et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a detector having the added advantage of sensitivity at the level of a single molecule via exponential replication of the target polynucleotide to produce up to a billion copies of a single target molecule as explicitly taught by Lizardi et al (column 14, lines 40-41 and column 3, lines 48-50).

13. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Lizardi et al (U.S. Patent No. 5,312,728, issued 17 May 1994) as applied to claim 32 above, and further in view of Hashimoto (U.S. Patent Application Publication No. US 2001/0024788 A1, issued 27 September 2001).

This is a new rejection necessitated by the amendments.

Regarding claim 33, the detector of claim 32 is discussed on pages 9-11 above. While Lee et al teach the electrode comprises a metal (page 8, lines 15-21), neither Lee et al nor Lizardi et al teach gold electrodes.

However, Hashimoto teaches a nucleic acid carrier for electric detection of nucleic acids (Abstract) comprising gold electrodes and immobilized thiolated nucleic acids with the added advantage that gold is preferable for immobilizing sulfur-bearing nucleic acids because of the high affinity of gold for sulfur (paragraph 0032).

It would therefore have been obvious to a person or ordinary skill in the art at the time the claimed invention was made to have modified the detector comprising metal electrodes as taught by Lee et al in view of Lizardi et al with the gold electrodes as taught by Hashimoto with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a detector having the added advantage of having high affinity immobilization of nucleic acids to the electrodes as explicitly taught by Hashimoto (paragraph 0032).

Response to Arguments

Applicant's arguments on pages 8-10 of the Remarks regarding the teachings of Lizardi et al have been fully considered but they are not persuasive for the reason(s) listed below.

A. It is noted that Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Thus, the teachings of Lizardi et al are solely relied upon for the teachings of the further internal structure of the second region.

B. Applicant argues on pages 9-10 of the Remarks that Lizard et al do not teach disruption of the first and second nucleotide sequences to release the first loop and form a second loop.

However, Lizardi et al do in fact teach disruption of the first and second nucleotide sequences to release the first loop and form a second loop; namely, Figure 13 shows that upon hybridization to oligonucleotide target 8, loop 31, which is the probe sequence, is hybridized to the target. Because

Lizardi et al teach switch sequences and probe sequences overlap (column 7, lines 47-55), part of 32, which is the first nucleotide sequence, also hybridizes to the target. The remaining part of 32, which is in the second region, hybridizes to part of 34, which is also part of the second region, thereby forming second loop 33 in the detectable ribozyme structure of Figure 13 (column 14, Example V). Lizardi et al also teaches the probes have the added advantage of allowing exponential replication of the target polynucleotide (column 14, lines 40-41). Thus Lizardi et al teach the elements of the probe not taught by Lee et al. As detailed in the rejections presented above, the probe of Lee et al has a first region in the form of the end that is immobilized to the electrode (i.e., claim 30), and a third region that is the second end of the probe, where the redox moiety is attached. Thus, Lizardi et al is solely relied upon for the internal structure of the second region of the probe.

C. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the replication of single target polynucleotide provides up to a billion copies of said target (column 14, lines 40-41 and column 3, lines 48-50). Thus, the threshold of sensitivity of the detector is extended to the level of a single molecule because replication amplifies the number of copies of the single target polynucleotide molecule in the sample to the level of a billion. Therefore, the ordinary artisan would have been motivated to modify the detector of Lee et al with the probe of Lizardi et al to provide the added advantage of increasing the threshold of sensitivity of the detector is extended to the level of a single molecule as taught by Lizardi et al.

D. It is noted that a prior art reference is considered as a whole and for all it stands for. Thus, the rejections listed above merely present a modified interpretation of the teachings of Lizardi et al

solely for the purpose of clarifying the reason to modify the device of Lee et al with the teachings of Lizardi et al.

Conclusion

14. No claim is allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

16. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

Robert T. Crow
Examiner
Art Unit 1634